Review Article

Renal Complications Following COVID-19 Vaccination: A Narrative Literature Review

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Abstract

Background: Renal complications have previously been reported with various vaccinations, including those for influenza and hepatitis. On a similar note, a spectrum of nephrological complications, both *de novo*, and flare-ups, were reported after immunization with various coronavirus disease 2019 (COVID-19) vaccines, causing concerns among patients as well as physicians. **Materials and Methods:** A systematic search of the literature published on renal complications seen post-COVID-19 vaccination was performed up to April 2022 using electronic databases such as PubMed and Google Scholar. **Result:** Immunoglobulin A (IgA) nephropathy, minimal change disease, glomerulonephritis, acute kidney injury, nephrotic syndrome, and anti-neutrophil cytoplasmic antibody-associated vasculitis were some of the renal complications reported upon administration of COVID-19 vaccines. The causality and underlying pathogenic mechanisms linking these complications and COVID-19 vaccination remain unclear. Nonetheless, a temporal relationship has been established with dysregulated T-cell response, transient systemic pro-inflammatory cytokine response, molecular mimicry, delayed hypersensitivity reaction to the vaccine, and other mechanisms such as hyperresponsive IgA, dysregulation of neutrophil extracellular traps were hypothesized as the possible mechanisms linking renal complications and COVID-19 vaccination. **Conclusion:** This review emphasizes the need for rigorous surveillance and reporting of the adverse events following COVID-19 vaccination and explores the underlying mechanisms instigating these renal complications in individuals vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Keywords: COVID-19 vaccine, pathogenesis, post-vaccination complications, renal complications

Introduction

Patients with renal diseases were prioritized to receive coronavirus disease 2019 (COVID-19) vaccinations, as the presence of kidney disease increases the risk of developing a severe COVID-19 infection upon exposure to the SARS-CoV-2. Owing to the compromised immune system found in patients with renal diseases, live replicating and microbial-vectored types of vaccines were advised to be avoided. Instead, inactivated replication-defective and viral-vectored vaccines were preferred to vaccinate these patients. BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and ChAdOxl nCoV-19 (Oxford-AstraZeneca) were so far listed as safe to be used in immune-compromised patients.[1]

On the flip side, reports of renal complications occurring after receiving COVID-19 vaccination came to light in recent times, following the mass vaccination drive initiated against SARS-CoV-2.[2] The occurrence of complications post-vaccination instigates concerns among the patients as well as the healthcare professionals. This raises a lot of queries such as:

- *What are the renal complications reported so far post-COVID-19 vaccination?*
- *Which COVID-19 vaccines were found to be associated with renal complications post-vaccination?*
- *Are these conditions de novo or flare-ups of the preexisting renal diseases?*
- *Is the occurrence of these renal complications causal or casual?*

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- *What are the possible underlying mechanisms explaining the occurrence of these complications post-vaccination?*
- *Is it safe to administer a follow-up dose, if a patient develops renal complications with the initial dose vaccination?*

The present review's objective was to answer these queries following a thorough search of the published literature available in Pubmed and Google Scholar electronic databases performed up to April 2022. All the case reports, case series, editorials, and other articles published related to the renal complications developed post-COVID-19 vaccination were reviewed. Articles available in the English language were included.

What are the renal complications reported so far post-COVID-19 vaccination?

A thorough search of the literature published in Pubmed and Google Scholar revealed the following renal complications reported post-COVID-19 vaccination:

- IgA nephropathy (IgAN)[2–12]
- IgA vasculitis with severe glomerulonephritis[13]
- De novo and relapsing necrotizing vasculitis[14]
- Minimal change disease (MCD)[15–18]
- Minimal change disease with IgAN[19]
- Minimal change disease with severe acute kidney injury[20]
- Minimal change glomerulonephritis[21]
- Membranous nephropathy (MN)[22-24]
- Anti-glomerular basement membrane antibody disease (Anti-GBM)[25]
- IgG4-related disease (IgG4-RD)[26]
- Lupus nephritis (LN)[27]
- Scleroderma renal crisis[28]
- Anti-neutrophil cytoplasmic antibody-associated glomerulonephritis[29]
- ANCA-associated vasculitis[30-32]
- ANCA-associated vasculitis presenting with rhabdomyolysis and pauci-immune crescentic glomerulonephritis[33]
- Myeloperoxidase-antineutrophilic cytoplasmic antibody-associated vasculitis (MPO-ANCA)[34]
- Anti-neutrophil cytoplasmic antibody-associated vasculitis with acute renal failure[35]
- Acute interstitial nephritis[36-39]
- Acute kidney injury (AKI)[10,40]
- Pre-renal AKI[41]
- COVID-19 vaccine-associated glomerular disease (CVAGD)[42-45]
- Acute tubular necrosis (ATN)[46]
- Acute tubulointerstitialnephritis[47-49]
- Nephroticsyndrome[50-54]
- New-onset pediatric nephroticsyndrome[55]
- Renal thrombotic microangiopathy[56]
- Focal segmental glomerulosclerosis[57]
- Glomerulonephritis[46,58]

Which COVID-19 Vaccines Were Found to be Associated with Renal Complications Post-Vaccination?

The recent literature review revealed that both mRNA and replication-defective viral vector vaccines were associated with at least any one of the renal complications, irrespective of the vaccination dose (i.e., both first and second) administered. A retrospective study identified patients who were hospitalized with de novo renal complications following COVID-19 vaccination and found that 17 patients had developed new onset nephropathy. These complications were seen within three months of administration of first and second doses of BNT162b2 (Pfizer-BioNTech), ChAdOx1 nCoV-19 (Oxford-AstraZeneca), and mRNA-1273 (Moderna) vaccines.[3] Acute kidney injury and nephrotic syndrome were reported following immunization with CoronaVac (Sinovac), a killed whole virus vaccine.[40]

The BBIBP-CorV/Sinopharm and Gam-COVID-Vac or Sputnik V/Gamaleya vaccines were seen with the development of glomerulopathies in patients vaccinated with the first dose.[59]

Are These Conditions De Novo or Flare-Ups of Preexisting Renal Diseases?

The occurrence of these renal complications post-COVID-19 vaccination could be either de novo or flare-ups of preexisting renal diseases.[14,49,60,61] There also exists the possibility of the unmasking of these renal complications in a previously healthy patient with subclinical or occult renal pathologies upon COVID-19 vaccination.[8,58] Hanna *et al.*[12] published a case of *de novo* gross hematuria, proteinuria, and acute kidney injury seen in a 17-year-old healthy male, less than 24 hours after second dose vaccination. Kidney biopsy revealed IgAN with cellular glomerular crescents and tubule interstitial scarring, indicating an acute exacerbation of a preexisting IgAN.

Is the Occurrence of These Renal Complications Post COVID-19 Vaccination Causal or Casual?

It is often challenging to establish a causal link between a particular vaccine and the adverse event seen following its administration, especially based on case reports alone. To assess the causality of adverse events following immunization (AEFI), various algorithms, causality assessment tools, and models were developed by certain organizations such as WHO and Brighton collaboration.[62] Global Advisory Committee on Vaccine Safety has recently proposed a checklist to be followed, after reporting any AEFI, to determine its causality.[63] The event checklist includes the following questions:

- Is there any strong evidence for other causes?
- Is there a known causal link with the vaccine or vaccination (vaccine product, vaccine quality, immunization error, and immunization anxiety)?
- If yes, was the event within a plausible time window following immunization?

- Is there any strong evidence against a causal link between the vaccine and the adverse events reported?
- In the patient with AEFI, did such an event occur in the past following the administration of a similar vaccine?
- In this patient with AEFI, did a similar event occur in the past independent of the vaccination?
- Could the current event have occurred in the patient with AEFI, without vaccination (background rate)?
- Does the patient with AEFI, have an illness, preexisting condition, or risk factor that could have contributed to the event?
- Was the patient with AEFI, taking any medication before vaccination?
- Was the patient with AEFI, exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product, etc.)?

The cases published so far failed to assess and ensure all of the abovementioned criteria to establish a definitive causal link between the COVID-19 vaccination and the subsequently developed renal repercussions. Villa *et al.*[64] have reported the first case of ANCA vasculitis following vaccination with AZD1222 (Oxford-AstraZeneca). They proposed a causality only based on temporal association and failed to demonstrate a direct link between renal complications and COVID-19 vaccination. Abdulgayoom *et al.*[52] presented a case of new onset minimal change nephrotic syndrome following the first BNT162b2 dose. They proposed that MCD development could be directly related to COVID-19 vaccination due to the following reasons:

- MCD onset was only four days after immunization indicating a more direct link rather than mere coincidence.
- An extensive patient workup revealed the presence of no secondary causes of MCD.
- Presence of existing literature on similar case presentations of MCD after administering influenza and hepatitis B vaccinations.
- The literature review revealed the case reports describing the occurrence of similar renal complications after covid vaccine administration.

So far, the causal relationship is explained mainly based on the temporal association between renal complication occurrence and administration of the COVID-19 vaccines. Additionally, the occurrence of similar AEFI with other similar vaccines against pathogens like influenza and hepatitis was also reported in the past. Systematic analysis of the adverse event reported following immunization using existing causality assessment tools would help in determining the causal link between renal complications and COVID-19 vaccination.

What are the Possible Underlying Mechanisms Explaining the Occurrence of These Complications Post-COVID-19 Vaccination?

The possible underlying pathogenic mechanisms explaining the occurrence of renal complications post-COVID-19 vaccination remains yet to be unclear. The temporality between these complications and the COVID-19 vaccination could be elucidated by certain proposed theoretical mechanisms as described in the literature, such as in [Figure 1]:

- Dysregulated T-cell response
- Transient systemic pro-inflammatory cytokine response
- Molecular mimicry
- Delayed hypersensitivity reaction to the vaccine
- Other possible mechanisms

Dysregulated T-cell response

A strong cell-mediated immune response was seen to be elicited following COVID-19 vaccination.[3,53] Many studies proposed that there could be aberrant activation of the immune system in genetically susceptible individuals,[20] causing a dysregulated T-cell response.[15,16,45] This was found to cause alterations in

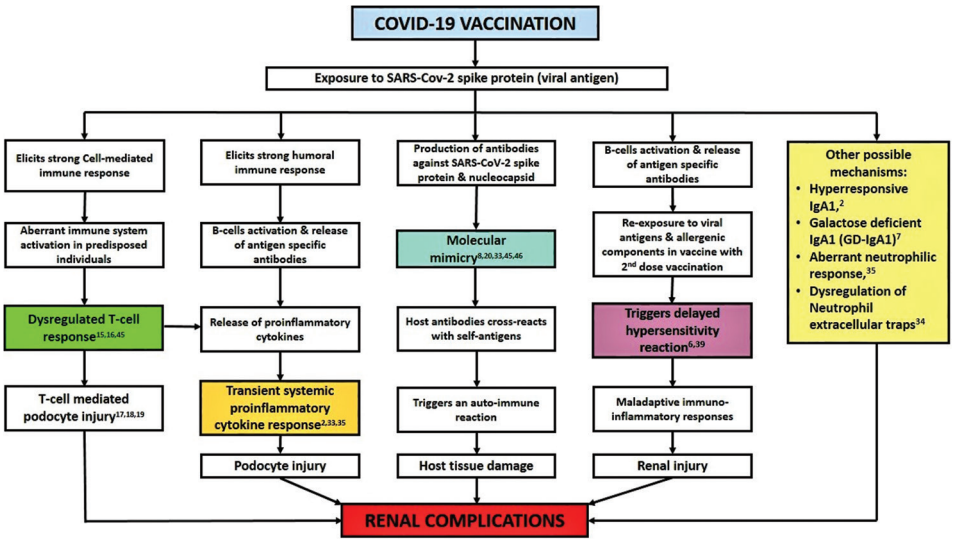

Figure 1: Possible pathogenic mechanisms linking COVID-19 vaccination and renal complications

glomerular permeability due to the production of glomerular permeability factor, causing diffuse foot process effacement.[16] This eventually leads to T-cell-mediated podocyte injury.[17-19]

Transient systemic pro-inflammatory cytokine response

The proinflammatory cytokines released following humoral and cell-mediated immune responses upon vaccination, could induce renal tissue injury.[2,33,35]

Molecular mimicry

Exposure to non-self "SARS-CoV-2" spike protein and nucleocapsid produces antibodies that cross-react with self-human antigens like transglutaminase 3, triggering an auto-immune reaction. This could aggravate or unmask the underlying autoimmune conditions.[8,20,33,45,46] Klomjit *et al.*[46] hypothesized the possibility of underlying immune dysregulation seen in a few individuals, could predispose them to develop renal complications following COVID-19 vaccination.

Delayed hypersensitivity to vaccine

Exposure to SARS-CoV-2 spike protein and allergenic components of vaccines such as PEG 2000 was found to activate B-cells and release antigen-specific antibodies. Upon second dose vaccination, re-exposure to these allergens could elicit a delayed hypersensitivity response in susceptible individuals. This leads to aberrant immune system activation with the release of proinflammatory cytokines, causing renal injury.[6,39]

Other possible mechanisms

Watanabe *et al.*[2] suggested the role of hyperresponsive IgA1 antibodies in the development of IgAN. Nihei *et al.*[7] hypothesized the effect of COVID-19 vaccination on galactose deficient IgA1 (GD-IgA1) through the stimulation of toll-like receptor (TLR-7). Abramson *et al.*[11] stated that the anti-glycan antibodies cross-reacting with preexisting under-galactosylated IgA1 and rise in levels of pathogenic IgA could play a role in the development of renal complications with COVID-19 vaccination. The possible role of aberrant neutrophilic response and NETosis has also been suggested. messenger RNA (mRNA) vaccination could elicit an aberrant neutrophilic response, which enhances with second dose immunization and further triggers antibodies such as myeloperoxidase-ANCA auto antibodies[33] and PR3 (a bactericidal protein expressed by neutrophil granules).[29] The cytokines released following COVID-19 vaccination could prime neutrophils and cause activation of neutrophil extracellular traps (NETosis).[34,35] Abnormalities in NETs regulation due to environmental and genetic factors could produce ANCA.[34]

Is It Safe to Administer a Follow-Up Dose, If a Patient Develops Renal Complications with the Initial Dose Vaccination?

Unveretal[40] reported the occurrence of the nephrotic syndrome within first week of receiving the first dose of the CoronaVac vaccine, which had improved with therapy. However, within one week of second dose vaccination, they found the return of edema with acute kidney injury and massive proteinuria. This raises concerns about whether it is safe to receive the subsequent dose of vaccine if any adverse events were reported following the initial dose administration. Conversely, Mochizuki *et al.*[15] reported a case of de novo minimal change disease in a 25-year-old woman after the first dose of Moderna mRNA-1273 vaccination, which had complete remission following steroid therapy. They have also found that there is no relapse of renal complications following second dose vaccination and suggested that it may be safe to administer the subsequent dose vaccination alongside immunosuppressive treatment to achieve complete remission of renal complications developed. However, as the patient was on steroids at the time of the second dose vaccination, the chances for the recurrence of the renal complications could have been lowered.

Li *et al.*[45] suggested a change in vaccine type for the follow-up dose vaccination to prevent the recurrence of renal complications. They also proposed that, if the renal complications were mild and resolved, follow-up dose administration could be recommended for the patients.

Conclusion

The occurrence of renal complications, *de novo,* and flare-ups, following the administration of COVID-19 vaccination, have already been established through the numerous cases reported so far. However, many questions remain unanswered due to a lack of adequate evidence.

The findings of the present literature review were:

- A diverse array of renal complications were observed post-covid-19 vaccination including IgAN, MCD, AKI, ATN, Nephrotic syndrome, Glomerulonephritis, etc.,
- These complications were reported following the administration of mRNA and replication-defective viral vectored vaccines (first and second dose). BNT162b2 (Pfizer-BioNTech),[3] ChAdOx1 nCoV-19 (Oxford-AstraZeneca),[3] mRNA-1273 (Moderna),[3] CoronaVac (Sinovac),[40] BBIBP-CorV/Sinopharm,[59] Gam-COVID-Vac, and Sputnik V/Gamaleya[59] vaccines were a few with evidence of reports of renal adverse effects post-vaccination.
- The post-COVID-19 vaccination-associated renal complications were found to be either *de novo* in origin or flare-ups of the preexisting condition.[14,49,60,61] There also exists the possibility of the unmasking of these renal complications in a previously healthy patient with subclinical or occult renal pathologies upon covid vaccination.[8,58]
- The causality between COVID-19 vaccination and the occurrence of these complications remains to be unclear. So far, only a temporal relationship has been established and various pathogenic mechanisms, including molecular mimicry,[8,20,33,45,46] delayed hypersensitivity,[6,39] transient

systemic cytokine response,[2,33,35] dysregulated T-cell response,[15-20,45] and others, have been hypothesized to explain the occurrence of renal complications in COVID-19- vaccinated individuals.

- Most of the cases were found to be resolved with the administration of appropriate therapy such as steroids.[15] However, early diagnosis plays a crucial role in better management and preventing further worsening of these complications.

Physicians, especially nephrologists must be aware of the renal complications and counsel the patients to look out for the renal symptoms such as foamy urine, hematuria, and edema indicating renal functional anomalies, post-vaccination. As the benefits of COVID-19 vaccination outweigh, the dangers of developing renal complications upon its administration, immunizing patients against SARS-CoV-2 is highly recommended. Nonetheless, it is advisable to follow stringent surveillance for the AEFI, develop guidelines for the diagnosis, and management strategies of such events, and instigate further research into the molecular mechanisms that underpin the causal link between renal complications and COVID-19 vaccination.

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Conflicts of interest

There are no conflicts of interest.

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